Targeted therapy in brain metastasis

TARGETED THERAPY IN BRAIN METASTASIS

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Abstract

Purpose of review: To review the state of the art and new developments in the field of targeted agents for brain metastases.

Recent findings: The huge amount of information on new molecular compounds and the advances in understanding the molecular pathways that mediate brain colonization have led to an increase of interest in preclinical and clinical investigations in the field of brain metastases. Targeted therapies can be employed either on established brain metastases or in a prevention setting. Targeting angiogenesis is an attractive approach. Up to date, large clinical trial datasets have shown that antiangiogenic agents do not increase the risk of bleeding into the brain. Bevacizumab (an anti-VEGF agent) is undergoing investigation in clinical trials on brain metastases from non-small cell lung cancer (NSCLC), breast cancer and melanoma. Sunitinib, a multitarget small molecule tyrosine kinase inhibitor (TKI), is a promising agent in brain metastases from renal cell cancer. The EGFR inhibitors gefitinib and erlotinib have a definite activity in brain metastases from NSCLC with activating EGFR mutations. Regarding HER2-positive breast cancer patients with established brain metastases, lapatinib (small molecule TKI) seems particularly active in association with capecitabine. Lapatinib alone is attractive in the prevention setting. Brain metastases from melanoma with BRAF V600E mutations respond to a specific inhibitor, such as vemurafenib. The immunomodulator ipilimumab is also active on brain metastases from melanoma.

Summary: The use of targeted agents in brain metastases from solid tumors is promising. The setting of prevention will be probably expanded in the next years. Well designed clinical trials with proper endpoints are needed.

INTRODUCTION

Brain metastases occur in up to 40% of cancer patients and represent a major cause of mortality and morbidity [1*]. The majority of brain metastases originate from primary cancers in the lung (40–50%), breast (15–25%) and melanoma (5–20%). The incidence of brain metastases has raised as a result of a better detection of oligometastases by MRI, increase of survival of cancer patients because of progress in the treatment of the systemic disease and aging population.

The standard management of patients with brain metastases has been optimized over time, owing to technical improvements in surgery and radiation therapy, and a better definition of prognostic factors that has led to a

more accurate patient selection [2*,3*]. The role of chemotherapy with cytotoxic drugs is limited to palliation, and the efficacy depends on the chemosensitivity of the primary tumor [4].

Targeted therapies have been initially employed in primary cancers, based on the identification of molecular targets critical for tumor growth. More recently, the increased amount of information on new molecular compounds and the advances in understanding the molecular pathways that mediate brain colonization have led to a new interest in both preclinical and clinical investigations in the field of brain metastases [5*–7*].

TARGETED THERAPIES ON ESTABLISHED BRAIN METASTASES

Most clinical trials enrolled patients with established brain metastases who have progressed after whole-brain radiation therapy (WBRT). Less frequently targeted agents, either alone or in combination with WBRT, have been investigated in newly diagnosed brain metastases.

KEY POINTS

- Targeting angiogenesis is an evolving approach, with compounds such as bevacizumab, sunitinib, sorafenib and cilengitide being actively investigated.
- Response of NSCLC brain metastases to EGFR inhibitors is highly dependent on the presence of activating EGFR mutations.
- Among HER2-positive breast cancer patients, lapatinib in combination with capecitabine is active in the treatment of established brain metastases.
- An impressive rate of responses has been reported with the immunomodulator ipilimumab in brain metastases from melanoma, and specific BRAF inhibitors are being investigated.
- New prevention strategies and designing appropriate clinicotranslational studies are a challenge for the future.

Graphic Box 1

Targeting angiogenesis

In the past, patients with brain metastases have been largely excluded from clinical trials with antiangiogenic agents based on concerns regarding the risk of central nervous system (CNS) hemorrhage. However, recent reviews of large clinical trial datasets, retrospective and prospective studies have shown that patients with and without CNS metastases are at a similar risk of bleeding into the brain (0.8–3.3%), independent of antiangiogenic therapy [8–11]. Several phase I and II studies on bevacizumab alone or combined with other antineoplastic agents are ongoing in brain metastases from non-small cell lung cancer (NSCLC), breast cancer and melanoma. Trials employing anti-VEGF (vascular endothelial growth factor) agents (bevacizumab and cediranib) in brain metastases must monitor their potential proinvasive effects, as already demonstrated in glioblastoma. Sunitinib is an oral, small molecule, tyrosine kinase inhibitor (TKI) that targets the VEGF receptors 1 to 3 and the platelet-derived growth factor (PDGF) receptors α and β, and is able to cross the blood–brain barrier (BBB) rapidly [12]. The drug is registered for the treatment of advanced

renal cell cancer (RCC) and has yielded an overall response rate of 12% among 213 patients with brain metastases compared with 17% in the overall population of 3464 patients [13]. More recently, it has been reported that two out of six patients with RCC and newly diagnosed brain metastases (small, asymptomatic and without hemorrhage on MRI) achieved a near complete response (CR) to therapy with sunitinib with a duration of 23+ and 47+ months [14*]. A phase II study in patients with NSCLC and irradiated brain metastases [15] has shown a marginal antitumor activity [partial response (PR) 1.6%, median progression-free survival 9.4 weeks and overall survival (OS) 25.1 weeks]. Sunitinib is undergoing investigation in patients with brain metastases from breast cancer and melanoma. Other antiangiogenic agents, that are investigated in phase I and II trials on brain metastases, include sorafenib (miscellanea and kidney cancer) and cilengitide in lung cancer.

Targeting specific tumor types

Over time, clinical trials have increasingly investigated new agents that target specific molecular pathways in specific tumor types.

Non-small cell lung cancer

Between 10 and 25% of NSCLC patients (mainly adenocarcinomas) carry activating EGFR (epidermal growth factor receptor) mutations, with the highest prevalence (up to 55%) in never-smoking women from East Asia. Brain metastases from NSCLC have been shown to respond to oral EGFR TKIs gefinitib and erlotinib. Response rates (complete and partial) after gefinitib range from 10 to 38% with a median duration of response of 9–13.5 months, and the latency between the start of treatment and appearance of response is short (~1 month) [16–20]. Similar findings have been documented with erlotinib [21–24,25*,26]. As for extracranial disease, response to EGFR inhibitors is highly dependent on the presence of activating EGFR mutations [25*,27]. Chemo-naïve patients seem particularly responsive: among 23 Asian never smokers with brain metastases from NSCLC receiving first-line gefitinib or erlotinib, a 70% CNS response rate was observed [28], and all seven patients with brain metastases and chemo-naïve, advanced-stage, NSCLC achieved an objective CNS response [29]. Moreover, patients with brain metastases from EGFR-mutant NSCLC have improved overall survival compared with EGFR wild-type tumors when receiving an EGFR inhibitor [30]. EGFR inhibitors can be safely administered concurrently with WBRT [31,32]. A recent phase II randomized study in brain metastases from NSCLC, comparing WBRT plus gefinitib vs. WBRT plus temozolomide (TMZ), has failed to show any advantage (OS 6.3 months in the gefinitib arm and 4.9 months in the TMZ arm), despite the fact that the majority of patients were previously untreated and with a relatively good performance status [33*]. In the UK, a phase II trial comparing WBRT plus placebo versus WBRT plus erlotinib has been completed, and results are awaited for late 2012. Erlotinib seems to produce higher CSF levels than gefinitib [34*], and therefore could be preferable. In about 4% of patients with NSCLC, an ALK (anaplastic lymphoma kinase) rearrangement occurs: crizotinib is an oral selective inhibitor of activated ALK, leading to objective response or stabilization in most patients harboring this molecular alteration [35]. There are no data on the activity of crizotinib in patients with brain metastases so far: however, a poor penetration of the agent into the brain could limit the potential efficacy [36].

Breast cancer

The risk of developing brain metastases among patients with breast cancer is higher for tumors that are HER2 positive or triple negative (i.e. lacking expression of HER2, estrogen and progesterone receptors), or of the basal-like subtype. HER2-positive patients (up to 25% of the overall population) have the greatest risk

(especially if estrogen/progesterone receptor negative) [37]. The frequency of brain metastases among HER2-positive patients treated with trastuzumab (a monoclonal antibody targeting HER2) in the metastatic setting is between 25 and 40% [38–42,43*]; similarly, when analyzing large phase III trials in the adjuvant setting, CNS metastases are significantly increased in the trastuzumab-containing treatment arms compared with the nontrastuzumab-containing arms [44**]. Moreover, the brain seems to be more frequently the first site of relapse in patients treated with trastuzumab, whether in the metastatic or adjuvant setting [45*]. A combination of factors likely explains the increased incidence of CNS disease in these patients, including a high propensity of HER2 cells for brain colonization [46,47], and improved control of systemic disease with trastuzumab, which has poor BBB penetration [48], and therefore is not able to target micrometastases that are protected by an intact BBB. It is interesting to note that the HER2 status seems to be consistent between matched primary tumors and brain metastases in the majority of patients [49]. This latter point, along with the well known disruption of the BBB in lesions greater than 1 cm of diameter, could argue in favor of some role of trastuzumab in the treatment of established brain metastases. In this regard, some recent studies have reported that trastuzumab improves the prognosis of HER2-positive patients with brain metastases [43*,50,51,52*].

Lapatinib is an orally dual TKI targeting EGFR and HER2 pathway, and is primarily used for the treatment of trastuzumab-resistant advanced breast cancer. Phase II trials have evaluated lapatinib as a single agent in patients with progressive HER2-positive breast cancer and brain metastases despite standard radiotherapy [53,54], and showed only modest efficacy with objective responses in 2 and 6% of patients, respectively. Minor responses were reported in a further 18 and 21% of patients. Interestingly, responding patients had an improved time-to-progression compared to no responding patients. The combination of lapatinib and capecitabine, an active drug against metastatic breast cancer, has yielded better results, with CNS responses ranging from 18 to 38% in the refractory setting (after previous WBRT) [54–56,57*,58*]. Only one study addressed the role of lapatinib plus capecitabine prior to WBRT and showed an impressive CNS response rate of 67%, with a median time to progression of 5.5 months and a median time to WBRT of 8.3 months [59*]. These results could open the door for studies comparing WBRT versus lapatinib plus capecitabine as initial therapy for HER2-positive patients. The combination of lapatinib with topotecan is not active and associated with excess toxicity [58*]. Another approach could be the association of lapatinib alone or combined with capecitabine with WBRT; preliminary results in terms of response are encouraging, but there are still issues of tolerance [60]. The RTOG is in the process of initiating a randomized phase II trial comparing WBRT alone with WBRT plus lapatinib.

PARP inhibitors include compounds, such as iniparib, olaparib and veliparib, that target the PARP pathway involved in the DNA single-strand break repair after radiotherapy and chemotherapy. These drugs have shown activity in triple-negative and BRCA-deficient breast cancer [61*]. In particular, iniparib, which is an intravenously administered drug, has been shown to favorably impact PFS and OS in a phase II trial on triple-negative and BRCA-deficient breast cancer patients [62], and is currently investigated (phase II trial), in combination with irinotecan, on triple-negative breast cancer brain metastases.

Melanoma

Up to 60% of melanomas carry an activating mutation in the gene encoding BRAF, a serine-threonine protein kinase. More than 85% of BRAF mutations are of the V600E type, which leads to constitutive kinase activity of BRAF and downstream activation of mitogen-activated protein kinase (MAPK) pathway, thereby enhancing the proliferative and metastatic capacity of the tumor. BRAF V600E mutations can now be easily detected immunohistochemically by the mutation-specific monoclonal antibody VE1 [63*] and seem consistent between primary melanomas and distant metastases [64*]. Vemurafenib, a specific inhibitor of

BRAF V600E mutated protein, has yielded response rates of up to 70% with improved PFS and OS in BRAF V600E mutated metastatic melanoma patients [65**]. Phase II trials investigating vemurafenib in patients with melanoma and brain metastases are ongoing, and an activity has been preliminarily reported [66*]. Recently, a case of successful use of vemurafenib in a child with metastatic melanoma to the brain has been described [67*]. In a phase I/II study, using another BRAF inhibitor (dabrafenib) in metastatic melanoma, all seven patients with previously untreated brain metastases showed CNS tumor shrinkage, including three CRs, and parallel extracranial responses were observed in most patients [68].

Another novel approach to treat advanced melanoma is the blockade of cytotoxic T-lymphocyte antigen-4 (CTLA-4), a molecule that downregulates the pathways of T-cell activation [69]. Ipilimumab is a fully human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 and potentiates antitumor immune responses [70]. In two phase III trials, ipilimumab has shown a statistically significant improvement in OS as monotherapy in previously treated patients [71**] and in combination with dacarbazine in treatment-naïve patients [72**].

An antitumor activity of ipilimumab in patients with brain metastases was originally suggested by Downey et al.[73], who treated 139 patients with stage IV melanoma: one of the 10 patients with brain metastases had a CR and two a PR. Two case studies have provided further support [74,75]. A recent retrospective analysis of a phase 2 trial [76*] has shown that 12 patients with previously treated stable brain metastases given ipilimumab had an overall survival of 14 months; moreover, two patients with partial response and one with stable disease survived for more than 4 years. In early 2012, an open-label, phase 2, multicenter U.S. trial [77**] has confirmed that ipilimumab has activity in patients with melanoma brain metastases, particularly when they have stable and asymptomatic metastases that do not need steroids: disease control (CR + PR + SD) after 12 weeks of treatment was 16% in the cohort of asymptomatic patients without steroids compared to 5% in the cohort of symptomatic patients receiving steroids. Importantly, the investigators did not report any neurological deterioration as an effect of an inflammatory response to treatment in the CNS, even in patients who received prior radiation therapy. The possibility remains that steroid treatment at the initiation of ipilimumab could abrogate or downmodulate the immune response. Ipilimumab has similar activity in CNS and non-CNS lesions: an explanation is that T cells could pass through an intact BBB [78] and promote an antitumor T-cell response and necrosis in brain lesions similar to that observed in extracranial lesions [79]. Further studies could assess the combinations of ipilimumab with radiotherapy, conventional cytotoxic drugs, such as TMZ or fotemustine [80], BRAF inhibitors and other emerging immunotherapies [81*,82*].

Factors limiting the efficacy of targeted agents

Overall, responses of established brain metastases to targeted agents have not been achieved in the majority of patients, and the reasons are multifactorial [83**]. Targeted agents may have still a limited capacity to cross the BBB, as in the case of cytotoxic drugs [84]. A recent study performed on experimental brain metastases from breast cancer [85*] has shown that brain metastases concentration of lapatinib was seven-fold to nine-fold greater than surrounding brain tissue, but average lapatinib concentration in brain metastases was 10–20% of that in peripheral metastases, and only in a subset of brain lesions (17%) did lapatinib concentration approach that of systemic metastases. Drug efflux pumps markedly contribute to the lack of brain permeability of compounds such as gefinitib, erlotinib, lapatinib, sunitinib and sorafenib [86*,87]. Many molecular therapeutics are cytostatic and not cytotoxic, and thus not enough tumor cells in a lesion are killed to achieve a clinical response. Moreover, the increased interstitial fluid pressure from edema limits drug distribution.

PREVENTION STRATEGIES

Almost all of the preclinical molecular compounds that have been reported to date were tested in a prevention setting and, overall, the studies have shown that prevention of the outgrowth of brain metastases is feasible. In a prevention scenario, a partially permeable targeted drug could potentially reach and control the outgrowth of micrometastases [88*]. Experimental models have shown that bevacizumab may prevent early angiogenesis and induce prolonged dormancy of micrometastases [89,90*] and the VEGF antagonist cediranib may inhibit brain metastasis formation [91]. Lapatinib, vorinostat and pazopanib are able to prevent the formation of metastases by brain-tropic breast cancer cells [92*,93,94*]. The selective PLK1 inhibitor GSK 46I1364A, in a xenograft model of breast cancer brain metastases, inhibits the development of large brain metastases and prolongs the survival in comparison to untreated animals [95].

Limited clinical data also support the hypothesis that prevention of brain metastases is more achievable than significant shrinkage of established lesions. A long-term follow-up from the metastatic breast cancer trial of lapatinib plus capecitabine versus capecitabine alone reported a significant reduction in the incidence of metastases in the brain as first site of relapse after combined treatment [96]. A retrospective review of a subcohort of patients with advanced EGFR-mutated NSCLC treated with gefinitib or erlotinib reported 1-year and 2-year CNS relapse rates of 6 and 13%, respectively, these rates being much lower than historical data [97]. A retrospective analysis of the clinical trial data from sorafenib in patients with RCC and brain metastases demonstrated a 75% prevention of brain metastases development, compared with 4% response rate on established metastases [98]. A recent review of patients enrolled in a phase III trial on RCC (TARGET trial) revealed a significant lower incidence of brain metastases in patients who received sorafenib (3%) than in those who received placebo (12%) [99]. The protective effect of TKIs (sorafenib, sunitinib and pazopanib) from metastatic RCC involvement of the brain has been recently outlined [100*].

Ultimately, for both primary and secondary prevention studies, in addition to the promising new agents in preclinical models, the major challenge is the identification of patients at highest risk of developing brain metastases because of tumor and host factors. Up to date, only HER2-positive breast cancer patients have entered prevention trials to better define the role of lapatinib.

CHALLENGES IN DEVELOPING TRIALS ON TARGETED AGENTS IN BRAIN METASTASES

The design of clinical trials on targeted agents in brain metastases poses several problems [101*]. The choice of endpoints is influenced by factors such as the patient population (in particular regarding the different natural history of systemic disease and brain metastasis among different solid tumors), the type of trial (phase 0, phase I, phase II and phase III) and the setting (treatment of established brain metastases or prevention). The ideal measure of drug activity in the brain is the assay of target modulation within the tumor in the resected tissue of patients treated preoperatively. Moreover, advanced neuroimaging techniques may provide valuable surrogate pharmacodynamic information [102]. Objective response has been commonly used as primary endpoint for phase II trials in patients with brain metastases, being a possible surrogate for other markers of clinical benefit, such as neurological status, neurocognitive decline or neurological deterioration free-survival. Unfortunately, none of the standard response criteria (Recist, WHO, MacDonald and RANO) were designed specifically for brain metastases. There is a need to standardize the MRI criteria for lesion measurement (tumor area vs. volume) and definition of the entity of shrinkage required to quality for response, and to include steroids and neurological symptoms in the response criteria. Special drugs (antiangiogenic agents and immunomodulators) will require specific adaptations. A clear distinction between intracranial, extracranial and overall progression-free survival is important. When the concurrent systemic

disease is controlled by a standard systemic regimen, the safety (not only the efficacy) of the association of an investigational agent for brain metastasis must be carefully evaluated.

As the number of experimental agents increases and available resources contract, new trial designs could be required: for instance, adaptive randomization can make clinical trials more efficient in reaching endpoints with fewer patients than required with conventional randomization [103].

All these issues are now being discussed within the international RANO (response assessment in neurooncology) working group, which already developed response criteria for primary brain tumors [104].

CONCLUSION

At present, definite data on the clinical activity of targeted agents in brain metastases are lacking, as virtually no well designed clinical trials have been performed. There is a need to understand novel targets and secondary resistance mechanisms. The combination of agents that target signal transduction pathways with those that modulate the immunological response to tumor is promising. Ultimately, the concept of prevention (primary or secondary) is the most appealing.

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Conflicts of interest

All the authors have no conflicts of interests.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

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